

**eP1709****The response of colorectal cancer cells to 5-Fluoruracil and Oxaliplatin Mimicking the clinical schedule involves the interplay among apoptosis, senescence and cytoprotective autophagy**

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Colorectal cancer (CRC) is among the most common and aggressive cancers worldwide. Primary therapy to CRC includes 5-Fluoruracil (5-FU) and Oxaliplatin (Oxa). Here, we aim to investigate the cellular mechanisms that mediate the response of CRC to the co-treatment with 5-FU and OXA, in a schedule that mimics the clinics, i.e. 48h of exposure to the drugs followed by two weeks before the second treatment. We repeated this cycle twice. Our main objective was to understand the outcome of CRC cells after the period of exposure to the drugs, in order to understand the mechanisms of response and resistance to the treatment. To this, we used the CRC human cell lines HCT116 and HT29. We found that acutely (48h), drugs did not show additive toxicity. However, chronically the combination had a strong additive effect, reducing both the growth of the population of cells and the growth of single cells in a clonogenic assay. 5-FU induced apoptosis, peaking 3d after treatment, while Oxa induced senescence 7 days after treatment, both in higher extent in HCT116 than in HT29 cells. The co-treatment induced an intense, transitory autophagy in both cell lines, reaching a peak 5 to 7 days after the treatment. Pharmacological suppression of autophagy during its peak of activation but not together with the chemotherapeutics strongly reduced cell growth. In summary, in the first cycle of treatment we found that the combination of 5-FU and OXA for 48h had additive toxicity along two weeks by the combination of apoptosis and senescence. However, both cell lines regrowth from day 7 after treatment onwards. In addition, suppression of autophagy strongly decreased cancer cells growth and clonogenicity. Then, we performed a second cycle of 5-FU and Oxa in the cells. Interestingly, cells were more sensitive to the second cycle of treatment, suggesting that resistance was not established. However, along the second cycle of treatment we found that senescent cells (induced in the first cycle of treatment) survived to the second cycle of treatment, while non-senescent cells were sensitive. Translationally, our data suggest that the rational modulation of autophagy may increase the toxicity of 5-FU plus Oxa co-treatment. Furthermore, we found that senescent cells, which can have a pro-tumor role due to their secretome, resisted to the second cycle of treatment, so that the elimination of these cells could improve the efficacy of the combined therapy with 5-FU and Oxa in CRC. Palavras-chaves: carcinoma coloretal, 5-Fluoruracil, Oxaliplatin